hyaluronate, zinc hyaluronate and cobalt hyaluronate.

Please amend claim 10 as follows, written in a "clean" format:

10. (Amended) The solid lipophilic microparticle of any one of claims 1 to 9, which further comprises a water-soluble excipient.

Please amend claim 11 as follows, written in a "clean" format:

11. (Amended) The solid lipophilic microparticle of claim 10, wherein the water-soluble excipient is selected from the group consisting of a carbohydrate, a protein, an amino acid, a fatty acid, an inorganic salt, a surfactant, poly(ethylene glycol) and a mixture thereof.

Q1 cancld.

Please amend claim 12 as follows, written in a "clean" format:

12. (Amended) A dispersion formulation prepared by dispersing the solid lipophilic microparticle of claim 1 in a lipophilic medium.

Please add new claims 21 and 22 as follows:

21. (Added) The solid lipophilic microparticle of claim 4, wherein the antigen is an attenuated, killed or recombinant antigen.

22. (Added) The solid lipophilic microparticle of claim 4, wherein the antigen is DNA, RNA, plasmid, CpG DNA or oligonucleotide extracted from the pathogen.

REMARKS

The Examiner's Office Action dated April 18, 2001 has been carefully reviewed. In view of the above amendments made to the claims and for the reasons provided below, early allowance of pending claims 1 to 22 is respectfully requested.

I. Claim Objections

As set forth above, claim 12 has been amended to refer back to claim 1 only in order to rectify the objected multiple dependency.

II. 102 Rejections

The Examiner has rejected claims 1 to 5, 7 and 10 to 18 under 35 U.S.C. 102(b) as being anticipated by Maniar et al. (WO 92/14449) and claims 1 to 6, 8 to 12 and 20 under 35 U.S.C. 102(e) as being anticipated by Poli et al. (US 5,795,566). However, the above 102 rejections are respectfully traversed for the reasons provided below.

1. Rejection of Claims 1 to 5, 7 and 10 to 18 under 35 U.S.C. §102(b)

i) Critical feature of the present invention

The present invention defined in pending claims 1 to 22, is directed to a microparticle having improved stability and capacity for effective delivery of a protein drug or an antigen and to a sustained-release formulation comprising said microparticle.

In particular, the present invention provides a solid lipophilic microparticle which has an average particle size ranging from 0.1 to 200 □, and comprises a lipophilic substance and an active ingredient, wherein the surface of the microparticle is coated with the lipophilic substance. The solid lipophilic microparticle may further comprise hyaluronic acid for preventing denaturation of the active ingredient.

The features of the solid lipophilic microparticle of the present invention recited in the currently pending claims can be summarized as follows:

(1) the active ingredient is not denatured and retains its full activity;

(2) the microparticle releases the active ingredient fully over a prolonged time

period; and

(3) it is easily dispersed in a lipophilic medium such as an oil, and the dispersion thus obtained has a low viscosity and retains the full activity of the active ingredient.

As fully described and corroborated in the present patent specification, the claimed solid lipophilic microparticle has numerous advantages over the conventional microparticles for drug delivery in terms of stability, sustained-release characteristics, injectibility and dispersability.

ii) Summary of the Maniar patent

The Maniar patent provides a biodegradable controlled release microparticle suitable for use in continuously delivering a biologically active protein such as growth hormone, and having enhanced stability with little or no loss of activity, wherein the microparticle comprises a biologically active protein or peptide dispersed in a fatty acid or fatty acid anhydride monomers or dimers and a stabilizer.

iii) Comparison of the present invention with the Maniar patent

In spite of the Examiner's view, the solid lipophilic microparticle of the present invention differs from the microparticles of the Maniar patent, as described below.

First, the fatty acid such as stearic acid (see Examples 1 and 9) or palmitic acid (see Example 7) used in the Maniar patent is a microparticle carrier for a controlled delivery of a biologically active protein or peptide. On the other hand, the lipophilic substance such as a fatty acid of the present invention is used for coating a solid microparticle of the active ingredient so as to confer lipophilicity on the surface of the microparticle. Such coating serves to improve the particle's dispersability and *in vivo* absorption rate.

Namely, the inventive microparticle of the present invention has the following features:

1) improved sustained-release characteristics endowed by the hydrophilic polymer coating,

2) retention of the full activity of a water-soluble protein/peptide drug, the denaturation of which is prevented by keeping the drug from contacting with an incompatible substance such as an organic solvent; and

3) improved dispersability and *in vivo* absorption rate attributable to the lipophilic coating.

In a prefered embodiment of the present invention, a microparticle coated with lecithin (microparticles 1 to 21) as a lipophilic substance disperses in an oil far better than a comparative microparticle having no coating (see Test Examples 5 and 6), and such dispersion has a superior injectability (see Examples 26 and 30).

However, the Maniar patent does not disclose or even suggest the above-mentioned advantages attainable by the lipophilic coating taught in the present invention. This cited document presents no more than a mere suggestion of a microparticle having improved and prolonged *in vivo* activity of a target protein by combining a stabilizer, the target protein and a carrier such as a fatty acid microparticle.

Accordingly, it is respectfully submited that the present invention is both novel and inventive over WO 92/14449.

2. Rejection of Claims 1 to 6, 8 to 12 and 20 under 35 U.S.C. §102(e)

i) Summary of the Poli patent

The Poli patent discloses bioadhesive microemulsions or liposomic dispersions containing

proteinaceous substances, especially calcitonin, that allow systemic, local or topical administration of drugs by the transmucosal route.

For this, this document provides a microemulsion composition suitable for administration of a protein or peptide drug, comprising the drug and a thermosetting agent, e.g., polyoxyethylene-polypropylene copolymer. The microemulsion contains water; a liphophilic alkyl ester of fatty acid; and one or more surfactants. In this microemulsion, the thermosetting agent is used to raise the viscosity at the body temperature so that said composition may attain a prolonged mucosal residence time and an enhanced drug absorption profile.

ii) Comparison of the present invention with the Poli patent

The Examiner has stated that the Poli patent teaches a lipophilic microparticle comprising a drug or an antigen and a lipophilic substance such as lecithin (see Example 4) or hyaluronic acid (see Example 3). However, a review of these Examples contained in the Poli reveals that the active ingredient is not encased within the lipophilic microparticles, as further discussed below.

Examples 1, 2 and 5: liposomic dispersions, wherein a water soluble drug (calcitonin) is present in the water phase;

Example 3: a gel formed by dissolving hyaluronic acid, a drug (posatirelin), and a polyoxyethylene-polyoxypropylene copolymer in water;

Example 4: a microemulsion, wherein a water-soluble drug (calcitonin) is present in the water phase; and

Example 6: a microemulsion, wherein a fat-soluble drug (nicotine) is dissolved in an oil.

In Example 3, hyaluronic acid is used simply as an absorption promoter. However, as is

clearly indicated in the present patent specification (see page 3, lines 6 to 20), a gel having hyaluronic acid at a concentration of several % is highly viscous, and cannot be used for injection. Further, since both the drug and hyaluronic acid dissolve in water, a hyaluronic formulation would rapidly release the drug, usually within a day, as is demonstrated in Comparative Test Examples 1 to 3 of the present invention.

In contrast to the Poli patent, the hyaluronic acid-containing microparticle of the present invention is prepared by: dissolving an active ingredient in an aqueous solution containing hyaluronic acid and a water-soluble excipient; spray- or freeze-drying the resulting solution to obtain solid particles; dispersing the solid particles in a solution containing a lipophilic substance; and then drying the dispersion (see page 9, lines 1 to 9).

In case of Example 4 in the Poli patent, a microemulsion is formed by mixing a lipophilic phase obtained by dissolving lecithin in a mixture of isopropyl myristate and ethyl alcohol together with an aqueous solution obtained by dissolving calcitonin in distilled water and adding polyoxyethylene-polyoxypropylene copolymer (Pluronic F127) thereto. Therefore, this Example uses an organic solvent, that tends to denature a protein drug, for dissolving biodegradable lecithin to form the lipophilic phase.

Accordingly, the Poli patent, which merely discloses liposomic dispersions or microemulsions that are formed by dissolving water-soluble drugs in water or fat-soluble drugs in oil, does not teach or suggest the solid lipophilic microparticle coated only its surface with the lipophilic substance that entails the advantages of the present invention, i.e., improved dispersability and *in vivo* absorption rate without the risk of denaturing water-soluble protein drug.

III. 103 Rejection

The Examiner has rejected claim 19 of the present invention under 35 U.S.C. §103(a) based

on the Poli patent.

However, as mentioned above, the solid lipophilic microparticle of the present invention is distinctly different from and has numerous unexpected advantages over the microparticles of the Poli patent.

Specifically, in the inventive oil-in-water emulsion formulation, the lipophilic microparticles containing an antigen remain in the oil phase, while another antigen remains in the aqueous phase: that is two different antigens are present separately in the aqueous phase and the oil phase, respectively, thereby preventing an undesirable interaction between them. In this connection, it is well known in the art that a mixed vaccine formulation prepared by adsorbing several antigens to alum in an aqueous solution suffers from a low vaccination effect due to undesirable interactions between the antigens.

Accordingly, the present invention as defined in claim 19 is neither obvious over nor easily derivable from the Poli patent.

IV. Conclusion

In view of the foregoing amendments and discussions, it is respectfully submitted that the present invention as defined in the pending claims 1 to 22 is in full compliance with all the statutory requirements, and, therefore, it is earnestly requested that the Examiner's objection and rejections be withdrawn and the pending claims be allowed in their present form.

Respectfully submitted,

Shahan Islam
Registration No. 32,507

DATE: September 17, 2001
ROSENMAN & COLIN LLP
575 Madison Avenue

New York, NY 10022-2585
(212) 940-8564

Version with markings to show changes made

A "marked up" version of claim 1 follows:

1. (Amended/Marked up) A solid lipophilic microparticle [having an average particle size ranging from 0.1 to 200 μm,] comprising a lipophilic substance and an active ingredient selected from the group consisting of a protein or peptide drug and an antigen, wherein the surface of the microparticle is coated with the lipophilic substance.

A "marked up" version of claim 2 follows:

2. (Amended/Marked up) The solid lipophilic microparticle of claim 1, wherein the average particle size is in the range of [1 to 50 μm] 0.1 to 200 μm.

A "marked up" version of claim 3 follows:

3. (Amended/Marked up) The solid lipophilic microparticle of claim 1, wherein the drug is selected from the group consisting of human growth hormone, bovine growth hormone, porcine growth hormone, growth hormone releasing hormone, growth hormone releasing peptide, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, macrophage-colony stimulating factor, erythropoietin, bone morphogenic protein, interferon, insulin, atriopeptin-III, monoclonal antibody, tumor necrosis factor, macrophage activating factor, interleukin, tumor degenerating factor, insulin-like growth factor, epidermal growth factor, tissue plasminogen activator and urokinase.

A "marked up" version of claim 4 follows:

4. (Amended/Marked up) The solid lipophilic microparticle of claim 1, wherein the antigen is obtained from one or more pathogens selected from the group consisting of [adenovirus type 4&7, hepatitis A virus, hepatitis B virus, hepatitis C virus, influenza A & B virus, Japanese B encephalitis virus, measles virus, epidemic parotitis virus, rubella virus,

polio virus, hydrophobia virus, chickenpox virus, yellow fever virus and human immunodeficiency virus; one or more pathogens selected from the group consisting of Bordetella pertussis, Borrelia burgdorferi, enterotoxigenic Escherichia coli, Haemophilus influenza type b, Mycobacterium leprae, Mycobacterium tuberculosis, Neisseria meningitidis A & C, Neisseria meningitidis B, Pseudomonas aeruginosa, Pseudomonas cepacia, Salmonella typhi, Shigella spp., Streptococcus pneumoniae and Vibrio cholerae; one or more pathogens selected from the group consisting of Coccidiodes immitis, Leishmania sp. and Plasmodium sp.; or one or more pathogens responsible for the disease selected from the group consisting of bovine blackleg, bovine epidemic fever, bovine anthrax, bovine Akabane's disease, bovine foot-and-mouth disease, bovine mammitis, bovine infectious nasotracheal inflammation, bovine viral diarrhea, bovine infectious gastroenteritis, porcine cholera, porcine epidemic diarrhea, porcine atrophic gastritis, porcine disease caused by pavovirus, porcine enteritis caused by rotavirus, chicken Newcastle disease, chicken Marek's disease, chicken encephalomyelitis, rabies, dog distemper, dog enteritis caused by pavovirus and dog infectious hepatitis, the antigen being an attenuated, killed or recombinant antigen; or DNA, RNA, plasmid, CpG DNA or oligonucleotide extracted from the pathogen] : adenovirus type 4&7; hepatitis A virus; hepatitis B virus; hepatitis C virus; influenza A & B virus; Japanese B encephalitis virus; measles virus; epidemic parotitis virus; rubella virus; polio virus; hydrophobia virus; chickenpox virus; yellow fever virus; human immunodeficiency virus; *Bordetella pertussis*; *Borrelia burgdorferi*; enterotoxigenic *Escherichia coli*; *Haemophilus influenza* type b; *Mycobacterium leprae*; *Mycobacterium tuberculosis*; *Neisseria meningitidis* A & C; *Neisseria meningitidis* B; *Pseudomonas aeruginosa*; *Pseudomonas cepacia*; *Salmonella typhi*; *Shigella* spp.; *Streptococcus pneumoniae*; *Vibrio cholerae*; *Coccidiodes immitis*; *Leishmania* sp.; *Plasmodium* sp.; and a pathogen responsible for bovine blackleg, bovine epidemic fever, bovine anthrax, bovine Akabane's disease, bovine foot-and-mouth disease, bovine mammitis, bovine infectious nasotracheal inflammation, bovine viral diarrhea, bovine infectious gastroenteritis, porcine cholera, porcine epidemic diarrhea, porcine atrophic gastritis, porcine disease caused by pavovirus, porcine enteritis caused by rotavirus,

chicken Newcastle disease, chicken Marek's disease, chicken encephalomyelitis, rabies, dog distemper, dog enteritis caused by pavovirus or dog infectious hepatitis.

A "marked up" version of claim 5 follows:

5. (Amended/Marked up) The solid lipophilic microparticle of claim 1, wherein the lipophilic substance is selected from the group consisting of a lipid, a lipid derivative, a fatty acid, a fatty acid derivative, a wax and a mixture thereof.

A "marked up" version of claim 6 follows:

6. (Amended/Marked up) The solid lipophilic microparticle of claim 5, wherein the lipid is lecithin, phosphatidylcholine, phosphatidylehanolamine or phosphatidylserine, and the lipid derivative is arachidoyl phosphatidylcholine or stearoyl phosphatidylcholine.

A "marked up" version of claim 7 follows:

7. (Amended/Marked up) The solid lipophilic microparticle of claim 5, wherein the fatty acid is myristic acid, palmitic acid or stearic acid, and the fatty acid derivative is glyceryl stearate, sorbitan palmitate, sorbitan stearate, sorbitan monooleate or polysorbate.

A "marked up" version of claim 8 follows:

8. (Amended/Marked up) The solid lipophilic microparticle of claim 1, which further comprises hyaluronic acid or an inorganic salt thereof.

A "marked up" version of claim 9 follows:

9. (Amended/Marked up) The solid lipophilic microparticle of claim 8, wherein the inorganic salt of hyaluronic acid is selected from the group consisting of sodium hyaluronate, potassium hyaluronate, ammonium hyaluronate, calcium hyaluronate, magnesium hyaluronate, zinc hyaluronate [or] and cobalt hyaluronate.

A "marked up" version of claim 10 follows:

10. (Amended/Marked up) The solid lipophilic microparticle of any one of [claims 1 and 8] claim 1 to 9, which further comprises a water-soluble excipient.

A "marked up" version of claim 11 follows:

11. (Amended/Marked up) The solid lipophilic microparticle of claim 10, wherein the water-soluble excipient is selected from the group consisting of a carbohydrate, a protein, an amino acid, a fatty acid, an inorganic salt, a surfactant, poly(ethylene glycol) and a mixture thereof.

A "marked up" version of claim 12 follows:

12. (Amended/Marked up) A dispersion formulation prepared by dispersing the solid lipophilic microparticle of [claims 1, 8 and 10] claim 1 in a lipophilic medium.